Recent studies found that high glucose increases the expression of tumor suppressor factor p53. And in the process of diabetic kidney disease (DKD) development p53 involves in regulating multiple signaling pathways. In addition, microRNAs (miRNAs) involve in many diseases pathogenesis. And miRNAs affect DKD development via adjusting multiple mechanisms. More importantly, p53/miRNAs signaling may participate in a variety of signaling pathways regulating kidney inflammation and fibrosis to control DKD pathological development. However, the mechanism of p53/miRNAs signaling participating in DKD pathological development is not yet clear. To illuminate the role of p53/miRNAs signaling may inspire a new thinking for elucidating the pathological mechanism of DKD, and provide a new theoretical basis for the prevention and treatment of DKD.

Keywords: p53; microRNAs; diabetic kidney disease


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Currently, with the improvement of people’s living standard and the changes in life style, the incidence of type 2 diabetes mellitus (T2DM) increased year by year. Diabetic kidney disease (DKD) is one of the most main microvascular complications of T2DM. And it is also one of the main reasons leading to end stage renal disease. More importantly, statistics data have shown that 20%-40% of people in patients with diabetes can develop DKD [1]. Consequently, early diagnosis and treatment of DKD could reduce or delay the onset of diabetic kidney damage, and improve the quality of patient’s life. It will provide important clinical significance.

Recent study found that high glucose raises the expression of p53 in kidney. Inhibiting p53 expression attenuates high glucose-induced acute kidney injury [2]. Besides, p53 and microRNAs (miRNAs) may regulate transforming growth factor-β1 (TGF-β1) expression in diabetes mice to affect the development of diabetes renal fibrosis [3]. However, the role of p53 regulating miRNAs in DKD pathological mechanism is not yet clear. To clear the role of p53/miRNAs signaling in DKD mechanism may help to provide new train of thought for elucidating the pathological mechanism of DKD. In this paper we will review the role of p53/miRNAs signaling in DKD.

The function of p53

Transcription factor p53 plays an important role in the process of inhibiting tumor. It inhibits tumor formation by
means of promoting DNA repair, preventing cell cycling, inducing cell aging and apoptosis \(^4, 5\). Sirtuin 1 (SIRT1) weakens the effect of p53 inhibiting tumor via deacetylation \(^6\), p53 activated by SIRT1 inhibitor increases the activity of nuclear factor \(\kappa B\) p65 (NF-\(\kappa B\) p65). Furthermore, it promotes cell apoptosis and the expression of pro-inflammatory factor as well \(^7\). SIRT1 may also suppress the activity of forkhead box O (FoxO) family via down-regulating p53 expression. And then it reduces reactive oxygen species (ROS) expression and apoptosis related to oxidative stress \(^8\). Activating adenosine monophosphate activated protein kinase (AMPK) phosphorylation can activate SIRT1, while suppressing AMPK activity can increase p53 acetylation \(^9\). It suggests that increasing the activity of AMPK phosphorylation may activate SIRT1 and attenuate the acetylation of p53, which results in inhibiting the activity of NF-\(\kappa B\) p65 and FoxO. Thereby, AMPK/SIRT1 signaling inhibits cell apoptosis and decreases the expression of pro-inflammation factor via down-regulating p53.

Although p53 often acts as a protective factor in cancer, it is a pathogenic molecule in many non-cancer diseases. In islet \(\beta\) cell cytoplasm p53 induces mitochondria dysfunction and impaired insulin secretion. As a result, it promotes diabetes development \(^10\). Besides, high glucose increases p53 expression via inhibiting AMPK/SIRT1 signaling pathways in liver cells, which causes lipid accumulation and insulin resistance \(^11\). Further study used metformin to activate high glucose-inhibited AMPK/SIRT1 signaling pathway. And results revealed that the expression of p53 protein significantly decreased. While over-expressed p53 reduces the expression of SIRT1 protein and inhibits metformin-activated AMPK signaling, accompanied by the decrease of triglycerides \(^12\). It suggests that there is a bidirectional interaction between p53 and AMPK/SIRT1 signaling in the pathogenesis and treatment of diabetes. However, the specific mechanism of p53 in diabetes and its complications is not yet clear.

**The function of microRNAs**

As a kind of small non-encoded RNA in body, miRNAs can regulate target gene expression at the translation level, which depends on base pairing between the ‘seed’ area of miRNAs and the 3’ untranslated regions of target genes’ mRNAs \(^13\). Bioinformatics research found that miRNAs can adjust more than 60% gene expression \(^14\). miRNAs play an important role in cell growth, differentiation, apoptosis, and metabolism process. In addition, miRNAs are also involved in the pathogenesis of many diseases, such as oxidative stress, cardiovascular, cancer, and diabetes \(^15,16\).

The expression of miR-200b, miR-429, and miR-200c increase significantly in diabetic vascular smooth muscle cells. And these miRNAs raise the expression of cyclooxygenase-2 (COX-2) and monocyte chemoattractant protein-1 (MCP-1), resulting in promoting inflammation \(^17\). miR-187 can decrease the expression of homeodomain-interacting protein kinase-3 (HIPK3), a factor regulating insulin secretion, and then reduce persistent hyperglycemia caused by glucose-stimulated insulin secretion \(^18\). Besides, high glucose promotes foxO3a expression via raising miR-30d expression, which raises the expression of inflammatory molecules and promotes cell apoptosis \(^19\). Research on diabetes patients also found that, with an increased level of urinary albumin, serum miR-130b level was significantly decreased and significantly negatively correlated with the serum levels of TGF-\(\beta\)1, hypoxia
inducible factor 1α (HIF-1α), and fibronectin (FN) \[^{20}\]. It prompts that miRNAs may influence the development of diabetes via adjusting multiple signaling mechanisms. Furthermore, it may play a role in DKD pathogenesis.

**p53/miRNAs and diabetes**

Although more and more evidences suggests that miRNAs play a regulatory role in metabolic disease, the mechanism of p53 participating in the process of miRNAs regulating metabolism is not clear yet \[^{18,19}\].

p53 can inhibit glycolysis by regulating miR-34, and then adjust the activity of a series of glycolytic enzymes such as hexokinase 1, hexokinase 2, and glucose 6 phosphate isomerase to enhance mitochondrial respiration \[^{21}\]. Cristianna et al. \[^{22}\] found that miR-199a-5p level has certain connection with diabetes development. Serine/threonine kinase (Akt) reduces miR-199a-5p expression, accompanied by higher SIRT1 expression. And overexpression of miR-199a-5p can reverse the change of SIRT1 expression \[^{23}\]. What’s more, studies found that p53 not only regulates the activity of Akt signaling pathways \[^{24}\], also regulates AMPK/SIRT1 signaling pathways involved in the pathogenesis of diabetes mellitus \[^{11,12}\]. It suggests that p53 may participate in the process of miRNAs regulating diabetes pathogenesis. It is important to further explore the mechanism of p53/miRNAs in the development of diabetes and its complications. (Fig. 1)

**p53/microRNA and diabetic kidney disease**

The early change of diabetic kidney damage is glomerular hemodynamics change, including high filtration and high perfusion damage \[^{25}\]. And the main pathological features of DKD are glomerular basement membrane thickening, extracellular matrix accumulation \[^{26}\], and interstitial inflammation \[^{27}\]. It promotes the process of kidney structure damage, such as glomerular sclerosis and interstitial fibrosis, which eventually leads to kidney failure. p53/miRNAs signaling may adjust a variety of signaling pathways to regulate DKD development. But the mechanism has not been fully elucidated.

**The role of p53/miR-34 signaling in DKD**

p53 regulates cell apoptosis via inhibiting miR-34 expression \[^{28}\]. Meanwhile, miR-34a can activate p53 to promote cell apoptosis by inhibiting SIRT1 expression \[^{29}\]. In energy metabolism, p53 regulates miR-34 expression to inhibit glycolysis, and then enhances mitochondrial respiration \[^{21}\]. Recent study has found that down-regulating miR-34 inhibits cell proliferation via inhibiting growth arrest-specific 1 (GAS1) in glomerular mesangial cells.
cultured with high glucose. What’s more, down-regulating miR-34 can alleviate glomerular hypertrophy in diabetes mice [30]. It suggests that p53 may play a role in the process of diabetic kidney damage via regulating miR-34 expression. (Fig. 2)

The role of p53/miR-192 signaling in DKD

The expression of miR-192 increases in patients with early DKD [31]. Furthermore, specifically inhibiting renal miR-192 expression alleviates renal fibrosis [32]. More importantly, study found that there is an interaction between p53 and miR-192, which regulates the downstream zinc finger E-box binding homeobox 1 (ZEB1) and TGF-β1 expression in diabetes mice renal. As a result, it affects the development of diabetic renal fibrosis [3]. It suggests that p53 may participate in the process of diabetic renal fibrosis through the mutual adjustment with miR-192, resulting in affecting the pathological development of DKD. (Fig. 2)

The role of p53/miR-199a and AMPK/SIRT1 signaling in DKD

High glucose raised p53 expression via inhibiting AMPK/SIRT1 signaling pathways [11]. Further evidence using metformin to activate AMPK/SIRT1 signaling can reduce p53 expression, while over-expressed p53 reduces the expression of SIRT1 [12]. Activating the phosphorylation of AMPK suppresses insulin resistance [33]. It also alleviates the activity of high glucose-stimulated mammalian target of rapamycin (mTOR)/p70S6K signaling pathways in glomerular mesangial cells, and thereby inhibits the expression of cell proliferation and fibrosis [34].

Besides, high glucose increases miR-199a-5p expression in glomerular mesangial cells [35]. Meanwhile, Akt reduces miR-199a-5p expression and raises SIRT1 expression. And over-expressed miR-199a-5p revises the expression of SIRT1 [23]. The ectopic expression of p53 induces miR-199a-3p transcription, and then affecting the restructuring of mice embryonic fibroblast cells [36]. We speculate that p53 may regulate DKD development by AMPK/SIRT1 signaling pathways, in which process miR-199a may play a certain role. (Fig. 2)

The role of p53/miR-21 and Akt/mTOR signaling in DKD

miR-21 negatively regulates the expression of p53 [37]. And p53 also influences miR-21 expression via regulating signaling transduction and signal transducer and activator of transcription 3 (STAT3) [38]. miR-21 expression appears significant change in early DKD [39]. Besides, miR-21 participates in diabetes related PI3K/Akt signaling and mTOR signaling [40]. However, its function and mechanism is still controversial. Zhao H et al. [41] considered that miR-21 regulates the activity of PI3K/Akt signaling to block glomerular stromal mast, which provides protection for early DKD [41]. Dey N et al. [41] considered that miR-21 may promote high glucose-induced mTOR expression and resulted in diabetic kidney damage. Research has found that activating p53 inhibits mTOR signaling [42]. Conversely, knocking out p53 gene significantly raises mTOR level and activates Akt protein [43]. More importantly, activating Akt/mTOR signaling increases DNA oxidative stress, and then promotes diabetic kidney damage [44]. It suggests that p53/miR-21 may participate in DKD development via regulating Akt/mTOR signaling. Further clarifying the mechanism is very important for clearing the pathogenesis of DKD. (Fig. 2)

The role of p53/miRNAs and TGF-β1/Smad signaling in DKD

High glucose activates TGF-β1/Smad signaling pathways to induce kidney ECM accumulating, which promotes interstitial fibrosis and glomerular mesangial expansion [25, 26]. There is a certain contact between miR-216, miR-217 and chronic kidney disease development. TGF-β up-regulates the expression of miR-216, 217 and activates Akt, resulting in contributing DKD development [45]. Kato M et al. [46] found that miR-192 could up-regulate these miRNAs expression. And p53 involved in the process of that miR-192 plays a role in the occurrence and development of DKD [3].

In addition, miR-224 not only plays a certain role in the development of diabetes, also plays a certain role in renal clear cell carcinoma [47]. More importantly, miR-224 participates in the process that TGF-β signaling pathways inhibits Smad4 expression. And p53 could inhibit miR-224 expression by combining the promoter of miR-224 coding gene. Conversely, down-regulating miR-224 expression activates p53 and inhibits Smad4 expression [48]. Therefore, we speculate p53/miRNAs may regulate the activity of TGF-β1/Smad signaling to affect DKD development. (Fig. 2)

Based on the foregoing analysis, p53 and miRNAs has some correlation with DKD development. p53/miRNAs signaling may participate in a variety of signaling pathways regulating the pathological of DKD. However, the role of p53/miRNAs signaling in the pathological mechanism of DKD is not yet clear. To illuminate the role of p53/miRNAs signaling may inspire a new thinking for elucidating the pathological mechanism of DKD, and provide a new theoretical basis for the prevention and treatment of DKD.

Conflicting interests
The authors have declared that no competing interests exist.

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